PATENT APPLICATION

DISORAZOLE POLYKETIDE SYNTHASE ENCODING POLYNUCLEOTIDES

RELATED APPLICATIONS

[0001] This application claims benefit of U.S. provisional patent applications no. 60/512,892 (filed October 20, 2003), 60/484,934 (filed July 2, 2003), 60/473,311 (filed May 22, 2003), 60/465,038 (filed April 23, 2003), 60/455,521 (filed March 17, 2003), and 60/431,272 (filed December 6, 2002) each of which is incorporated by reference its entirety.

FIELD OF THE INVENTION

[0002] The invention relates to materials and methods for biosynthesis of disorazole, disorazole derivatives, and other useful polyketides. The invention finds application in the fields of molecular biology, chemistry, recombinant DNA technology, human and veterinary medicine, and agriculture.

BACKGROUND OF THE INVENTION

[0003] Polyketides are complex natural products that are produced by microorganisms such as fungi and mycelial bacteria. There are about 10,000 known polyketides, from which numerous pharmaceutical products in many therapeutic areas have been derived, including: adriamycin, epothilone, erythromycin, mevacor, rapamycin, tacrolimus, tetracycline, rapamycin, and many others. However, polyketides are made in very small amounts in microorganisms and are difficult to make or modify chemically. For this and other reasons, biosynthetic methods are preferred for production of therapeutically active polyketides. See PCT publication Nos. WO 93/13663; WO 95/08548; WO 96/40968; WO 97/02358; and WO 98/27203; U.S. Pat. Nos. 4,874,748; 5,063,155; 5,098,837; 5,149,639; 5,672,491; 5,712,146 and 6,410,301; Fu et al., 1994, *Biochemistry* 33:9321-26; McDaniel et al., 1993, *Science* 262: 1546-1550; Kao et al., 1994, *Science*, 265:509-12, and Rohr, 1995, *Angew. Chem. Int. Ed. Engl.* 34: 881-88, each of which is incorporated herein by reference.

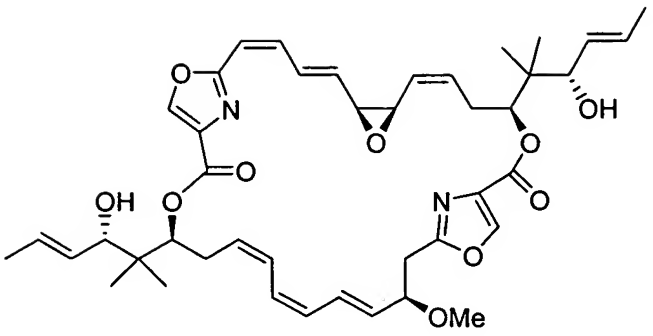
[0004] Biosynthesis of polyketides may be accomplished by heterologous expression of Type I or modular polyketide synthase enzymes (PKSs). Type I PKSs are large multifunctional

protein complexes, the protein components of which are encoded by multiple open reading frames (ORF) of PKS gene clusters. Each ORF of a Type I PKS gene cluster can encode one, two, or more *modules* of ketosynthase activity. Each module activates and incorporates a two-carbon (ketide) unit into the polyketide backbone. Each module also contains multiple ketide-modifying enzymatic activities, or *domains.* The number and order of modules, and the types of ketide-modifying domains within each module, determine the structure of the resulting product. Polyketide synthesis may also involve the activity of nonribosomal peptide synthetases (NRPSs) to catalyze incorporation of an amino acid-derived building block into the polyketide, as well as post-synthesis modification, or tailoring enzymes. The modification enzymes modify the polyketide by oxidation or reduction, addition of carbohydrate groups or methyl groups, or other modifications.

[0005] In PKS polypeptides, the regions that encode enzymatic activities (domains) are separated by linker regions. These regions collectively can be considered to define boundaries of the various domains. Generally, this organization permits PKS domains of different or identical substrate specificities to be substituted (usually at the level of encoding DNA) from other PKSs, by various available methodologies. Using this method, new polyketide synthases (which produce novel polyketides) can be produced.

[0006] It will be recognized from the foregoing that genetic manipulation of PKS genes and heterologous expression of PKSs can be used for the efficient production of known polyketides, and for production of novel polyketides structurally related to, but distinct from, known polyketides (see references above, and Hutchinson, 1998, *Curr. Opin. Microbiol.* 1:319-29; Carreras and Santi, 1998, *Curr. Opin. Biotech.* 9:403-11; and U.S. Pat. Nos. 5,712,146 and 5,672,491, each of which is incorporated herein by reference).

[0007] One valuable class of polyketides are the disorazoles. Disorazoles are a family of complex 26-membered bislactone macrocycles having two oxazole rings, which were first detected in the So ce12 strain of *Sorangium cellulosum* (Irschik *et al.*, 1995, *The Journal of Antibiotics,* 48:31-35). The So ce12 strain produces 29 congeners of disorazole compounds, with disorazole A (1) being the predominant product (see structure 1, below, and Figure 1).



(1)

[0008] Disorazole A shows remarkable activity against eukaryotic cells, having high mammalian cell cytotoxic activity (MIC ~ 3-30 pg/ml) and activity against different fungi, including filamentous fungi belonging to the Ascomycetes, Basidiomycetes, Zygomycetes, Oomycetes, and Deuteromycetes families (MIC ~ 0.1-1 μg/ml). In contrast, the compound is not highly active against yeast and bacteria. Jansen *et al.*, 1994, *Liebigs Ann. Chem.*, pp. 759-73.

[0009] The present invention provides polynucleotides and methods for biosynthesis of disorazoles, disorazole derivatives, and novel polyketides.

BRIEF SUMMARY OF THE INVENTION

[0010] In one aspect, the present invention provides a recombinant polynucleotide comprising a nucleic acid sequence that encodes a disorazole PKS domain or portion thereof. In one embodiment of the invention, the disorazole PKS domain is from *Sorangium cellulosum* (e.g., So ce12 strain). In one embodiment, a polynucleotide of the invention is expressed in a host cell under conditions in which one or more proteins encoded by a module of a disorazole PKS is produced. In one embodiment, disorazole or a disorazole-derivative is produced by the host cell upon expression of the polynucleotide of the invention. In an embodiment, the host cell is of a type that does not produce disorazole in the absence of expression of an exogenous polynucleotide, and in some embodiments the host cell does not produce any endogenous polyketide. One example of a suitable host cell is *Myxococcus xanthus*.

[0011] In another embodiment, a recombinant polynucleotides of the invention also comprises a coding sequence for one or more domains of non-disorazole polyketide synthase, to form a hybrid PKS. For example, a coding sequence for a module or domain (or portion thereof) of disorazole polyketide synthase may be combined with coding sequence from another PKS to form make a novel, hybrid or chimeric, PKS. Expression of such DNAs, in suitable host cells

leads to the production of synthases capable of producing useful polyketides, such as a disorazole analog or a useful synthon thereof, or a novel polyketide.

[0012] In an aspect, the invention provides an isolated recombinant polynucleotide that comprises a nucleotide sequence encoding a disorazole polyketide synthase (PKS) protein or a fragment comprising at least one domain of said PKS. In an embodiment, the polynucleotide hydridizes under stringent hybridization conditions to a polynucleotide having the sequence of SEQ ID NO:1 or its complement. In an embodiment, the polynucleotide comprises a sequence encoding a disorazole polyketide synthase protein selected from the group consisting of DszA, DszB, DszC, and DszD; a disorazole polyketide synthase module selected from the group consisting of module 1, 2, 3, 4a, 4b, 5, 6, 7, or 8; or a domain selected from the group consisting of an AT domain, a KS domain, an ACP domain, a KR domain, a DH domain, and an ER domain. In an embodiment, the invention provides a recombinant DNA molecule comprising a sequence of at least about 200 basepairs with a sequence identical or substantially identical to a protein encoding region of SEQ ID NO:1.

[0013] The invention provides vectors, such as expression vectors, comprising an aforementioned polynucleotide. In a related aspect, the invention provides a recombinant host cell comprising the vector. In an aspect the invention provides a recombinant host cell comprising an aforementioned polynucleotide integrated into the cell chromosomal DNA.

[0014] In an aspect, the invention provides an isolated polypeptide encoded by a recombinant polynucleotide of the invention. In an aspect, the invention provides a hybrid polyketide synthase comprising one or more polypeptides of a disorazole PKS and one or more polypeptides of a nondisorazole PKS .

[0015] In an aspect, the invention provides a method of producing a polyketide by growing the recombinant host cell under conditions whereby a polyketide synthesized by a PKS comprising a protein encoded by an aforementioned polynucleotide molecule is produced in the cell.

[0016] In an aspect, the invention provides a chimeric PKS that comprises at least one domain of a disorazole PKS, as well as a cell comprising such a chimeric PKS. A modified functional disorazole PKS that differs from the native disorazole PKS by the inactivation of at least one domain of the disorazole PKS and/or addition of at least one domain of a non-disorazole PKS is also provided, as well as a cell comprising the modified PKS.

[0017] The invention provides a recombinant expression system capable of producing a disorazole synthase domain in a host cell. The system comprises an encoding sequence for a disorazole polyketide synthase domain operably linked to control sequences effective in said cell to produce RNA that is translated into said domain. The invention provides a host cell modified to contain the recombinant expression system.

[0018] In an aspect, the invention provides a recombinant *Sorangium cellulosum* cell in which a *dsz*A, *dsz*B, *dsz*C, or *dsz*D gene is disrupted so as to reduce or eliminate production of disorazole.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figure 1 shows the structures of disorazoles A, B, C, D, E, F, G, H and I.

[0020] Figure 2 is a cartoon showing the relationship between inserts of several cosmid clones comprising disorazole PKS genes. "Phleo^{R}" indicates the site of insertion of a phleomycin-containing transposon into the PKS gene cluster.

[0021] Figure 3 shows the organization of the disorazole PKS genes *dsz*A, *dsz*B, and *dsz*C.

[0022] Figure 4 shows the organization of the disorazole PKS gene *dsz*D, encoding the AT/oxidoreductase bidomain protein.

[0023] Figure 5 shows the predicted product of the disorazole PKS (comprising the DszA, B, C and D proteins) in the absence of tailoring enzymes expressed in *Sorangium cellulosum*.

DETAILED DESCRIPTION OF THE INVENTION

[0024] Disorazoles have been identified as inhibitors of tubulin polymerization, inducing decay of microtubules. Disorazoles are synthesized by the disorazole polyketide synthase (PKS) or "disorazole synthase." The disorazole synthase comprises four polypeptides, called DszA, DszB, DszC, and DszD, which are encoded by the *dsz*A, *dsz*B, *dsz*C, and *dsz*D genes, respectively. In the following discussion, it will be clear from context whether a polynucleotide or DNA sequence, or a polypeptide or amino acid sequence is being referred to. There terms "nucleic acid" and "polynucleotide" are used interchangeably below. Examples of polynucleotides are DNA and RNA.

[0025] As described in the Examples below, recombinant DNAs encoding the disorazole biosynthetic genes have been cloned using a gene knockout strategy and characterized by

sequencing. Seven cosmid clones (pKOS254-190.1, pKOS254-190.2, pKOS254-190.3, pKOS254-190.4, pKOS254-190.5, pKOS254-190.6, and pKOS254-190.7) containing disorazole PKS encoding sequences were identified. Cosmids pKOS254-190.1 and pKOS254-190.4 were deposited on March 12, 2003, with the American Type Culture Collection (ATCC), Manassas, VA, USA, under the terms of the Budapest Treaty. Cosmid pKOS254-190.1 was deposited as K245-190.1 and assigned accession number PTA-5055. Cosmid pKOS254-190.4 was deposited as K245-190.4 and assigned accession number PTA-5056. Each of cosmids pKOS254-190.1 and pKOS254-190.4 contains most modules encoded in the disorazole PKS gene cluster, and the two cosmids together contain insert DNA that completely spans the disorazole PKS gene cluster. The relationships between the cosmid inserts are shown in Figure 2.

[0026] Table 1 shows the sequence of the disorazole polyketide synthase gene cluster and flanking sequences, with reference to Seq. ID NO:1 (see TABLE 6). The boundaries of the DszA, DszB, DszC and DszD encoding sequences are shown, along with the approximate boundaries of modules, domains and scaffold and linker regions. In addition, sequences encoding additional ketide synthase modules (KS7.2x, ACP7.2x, KS1p, ACP1p, KS2p and ACP2p) are encoded. In addition, several open reading frames in the gene cluster or flanking regions are shown: ORFs 0, 1, 2, 3, A, 0r, 1r, 2r, 3r, 4r, 5r, and 6r lie in the flanking region and ORF x1 lies in the intervening region between *dsz*C and *dsz*D. Abbreviations are: ketoreductase (KR), dehydratase (DH), enoylreductase (ER), nonribosomal protein synthase (NRPS), methyltransferase (MT), acyl carrier protein (ACP), serine cyclization domain and/or condensation domain (Cy), adenylation domain (A), peptidyl carrier protein (PCP) or thiolation (T) domain, oxidase domain (Ox), thioesterase domain (TE), acyltransferase domain (AT).

TABLE 1

DISORAZOLE POLYKETIDE SYNTHASE GENE CLUSTER AND FLANKING SEQUENCES

ORF, Module and Domain Boundaries (with reference to SEQ ID NO:1)	Description
>2..1357 (complement)	ORF0 (nter: 1-471 of 480 aa); homolog of ORF from Pseudomonas putida KT2440 [PP4696 (AAN70269)], putative nitrogen regulation protein NR(I)
1354..4365(complement)	ORF1_dsz; homolog of HisK from Pseudomonas putida KT2440 [PP4695 (AAN70268)]; putative sensory box histidine kinase
4831..5805(complement)	ORF2_dsz; homolog in family of known or putative phosphotransferases, including macrolide 2'-phosphotransferases: YcbJ_bacsu; MphB_bacha ; MphB_pTZ3723-ecoli; MphBM_pSR1-staau
5794...7089	ORF3_dsz; homolog in family of known or putative Ser/Thr protein kinases
8157..26192	DszA; (modules 1-4a)
8166..9440	KS1
11100..11720	DH1
12681..13520	KR1
13620..13823	ACP1
14067..15341	KS2
16662..17540	KR2
17829..18545	MT2 (CMT)
18768..18974	ACP2
19173..19376	ACP2bx
19491..20759	KS3
22020..22901	KR3
22911..23120	ACP3
23331..24626	KS4
25251..26117	DH4
26209..44979	DszB; (modules 4b-7, together with an additional PKS module: 7.2x)
26851..27693	KR4
27850..28056	ACP4
28234..29565	KS5
30381..30948	DH5
31651..32520	KR5
32533..32739	ACP5
32971..34266	KS6
35119..35760	DH6
36616..37479	KR6
37480..37683	ACP6
37834..39120	KS7
39712..40377	DH7
41293..42165	KR7
42196..42405	ACP7
42706..43986	KS7.2x
44542..44787	ACP7.2x

ORF, Module and Domain Boundaries (with reference to SEQ ID NO:1)	Description
44976..56363	DszC; DszC includes the NRPS (nonribosomal peptide synthase) module 8 and a thioesterase
45039..46493	Cy8#1
46530..47885	Cy8#2
47895..49445	A8
49530..49733	T8; PCP
49737..50492	Ox8
50628..51911	KS1p
52608..52814	ACP1p
52986..54278	KS2p
54978..55235	ACP2p
55404..56360	TE
56371..56431	probable hairpin terminator
56769..57590	ORFx1; compare ZP_00094564.1 (hypothetical protein [Novosphingobium aromaticivorans])
57756..60281	DszD; AT/oxidoreductase; bidomain protein
57756..58595	AT
58596..58931	linker
58932..60278	Oxred
60365..61042 (complement)	ORFA; homolog of S coelicolor SCO1915 (& 1 each from 2 corynebacterial genomes); hypothetical protein
63817..65103	ORF0r; 0352/7408; probable solute-binding lipoprotein; ABC transporter, periplasmic binding-protein; homolog of S. coelicolor SCO7408 & others
65100..66011	ORF1r; ABC permease unit
66128..66895	ORF2r; ABC permease unit; ORF1_brefu homolog
66892..69246	ORF3r; 1055; glycosyl hydrolase; homolog of S coelicolor SCO1055
69314..72526	ORF4r; 5685; glycosyl hydrolase; homolog of S coelicolor SCO5685
69389..69389	unclear sequence (1 bp)
72800..76072	ORF5r; 3820; serine-threonine protein kinase; homolog of S coelicolor SCO3820 complement(76084..76740) ORF6r
76084..76740	ORF6r

[0027] The organization of domains and modules of the disorazole PKS genes differs from that predicted based on the structure of disorazole and contains at least two unusual features. First, the sequenced disorazole biosynthetic gene cluster lacks a module that would load the acetate starter unit (loading module). Second, there are three modules, each consisting of only a KS and ACP domain, that are not predicted from the structure of disorazole. These are shown in Table 1 as KS7.2x-ACP7.2x, KS1p-ACP1p, and KS2p-ACP2p.

[0028] The absence of a loading module has not been previously reported for polyketide biosynthesis gene clusters. Possible explanations for its absence in the sequenced genes include (1) it lies in a region of the genome outside the disorazole gene cluster; and (2) the levels of acetyl-coA are high within the cell and permit the direct loading of the acetyl group onto the KS without the help of a loading domain. A situation similar to (2) occurs in the process of chemobiosynthesis also known as precursor directed biosynthesis (Jacobsen et al., 1997 "Precursor-directed biosynthesis of erythromycin analogs by an engineered polyketide synthase" *Science* 277:367-369). In precursor directed biosynthesis a mutation is introduced into the gene cluster that prevents the loading molecule from loading or being extended. A compound as an N-acetylcysteamine (SNAC) thioester is fed to the organism and becomes attached to the PKS enzyme. It then becomes extended by the PKS enzyme to make a variety of compounds depending on the SNAC that is fed to the organism. A third alternative is that module 1 functions as a loading and an extending module. In this case the AT loads the ACP of module 1. Since there is no starter unit, the KS functions to decarboxylate the malonate-ACP to give the acetyl-ACP. The acetyl group is then moved to the KS and is primed with the starter unit. The AT then loads another malonate group onto the ACP of module 1. Now in the presence of an acetyl starter unit attached to the KS, the KS can decarboxylate the malonate on the ACP and perform the condensation to give the appropriate molecule. This is then extended through the remaining PKS and NRPS modules.

[0029] The disorasole gene cluster encodes three modules, consisting of only a KS and ACP domain, that are not predicted from the structure of disorazole (shown in Table 1 as KS7.2x-ACP7.2x, KS1p-ACP1p, and KS2p-ACP2p. It is not clear whether or not these modules are required for biosynthesis of disorazole. Analysis of these domains revealed no obvious mutations that would indicate that they are inactive. It is possible that they are non-functional due to a (hypothetical) inability to interact with the AT domain. This could result in no extender unit being loaded, and the growing molecule would just be passed through these modules to either the NRPS or the TE. In certain embodiments of the invention, disorazole PKS polypeptides of the invention differ from native polypeptides by the deletion of all or part of these modules.

[0030] The invention provides purified, isolated and recombinant nucleic acid (e.g., DNA) molecules that encode a polypeptide or domain encoded in the disorazole PKS gene cluster and

flanking regions, as well as recombinant nucleic acid molecules with the sequence of the reverse complement the polypeptide-encoding strand. The reverse complement of a nucleic acid sequence can be easily determined by well known methods. As used herein, unless otherwise stated or apparent from context, reference to disorazole "PKS" includes the NRPS module. In one embodiment of the invention, the PKS domains are derived from *Sorangium cellulosum*, for example, the So ce12 strain. The invention provides purified or recombinantly produced polypeptides encoded by an aforementioned DNA molecule or comprising a sequence encoded by an aforementioned DNA molecule (such as chimeric and fusion polypeptides).

[0031] In an aspect the invention provides purified and isolated DNA molecules that encode all or a portion of one or more modules of disorazole PKS. Examples of such encoded modules include the loading module, and module 1, 2, 3, 4 (including 4a and 4b individually), 5, 6, 7, or 8 of the disorazole PKS.

[0032] In an aspect the invention provides purified and isolated DNA molecules that encode all or a portion of one or more domains of disorazole PKS. Examples of such encoded domains include disorazole synthase ketoreductase (KR), dehydratase (DH), enoylreductase (ER), ketosynthase (KS), nonribosomal protein synthase (NRPS), methyltransferase (MT), acyl carrier protein (ACP), serine cyclization domain and/or condensation domain (Cy), adenylation domain (A), peptidyl carrier protein (PCP) or thiolation (T), oxidase domain (Ox), thioesterase (TE), and acyltransferase (AT) domains from any of modules 1-8 of the disorazole PKS .

[0033] In an aspect the invention provides purified and isolated DNA molecules that encode a disorazole post-synthesis modification enzyme and/or has the sequence of an ORF selected from ORFs 0, 1, 2, 3, A, 0r, 1r, 2r, 3r, 4r, 5r, 6r, and x1. Examples of such post-synthesis modification enzymes include a cytochrome P450-like epoxidation enzyme and an O-methyltransferase.

[0034] In an aspect the invention provides purified and isolated DNA molecules that encode a polyketide synthase domain encoded by KS7.2x, ACP7.2x, KS1p, ACP1p, KS2p, or ACP2p or module comprising an aforementioned domain.

[0035] In one embodiment, the invention provides a disorazole PKS domain or module (or portion thereof), or disorazole modification enzyme, or other PKS domain or ORF in the disorazole PKS gene cluster or flanking region as encoded by a polynucleotide insert of pKOS254-190.1, pKOS254-190.2, pKOS254-190.3, pKOS254-190.4, pKOS254-190.5,

pKOS254-190.6, or pKOS254-190.7. In a preferred embodiment, the disorazole PKS domain or module or disorazole modification enzyme is encoded by a polynucleotide insert of pKOS254-190.1 or pKOS254-190.4.

[0036] Thus, as noted, in one aspect, the invention provides polynucleotides encoding a module or domain (or portion thereof) of a disorazole PKS biosynthetic enzyme, or disorazole modification enzyme. Accordingly, in a related aspect, the invention provides a recombinant polynucleotide encoding at least a fragment of a disorazole PKS protein comprising at least 10, 15, 20, or more consecutive amino acids of a protein encoded by the disorazole PKS gene cluster encoded by pKOS254-190.1 or pKOS254-190.4. In one embodiment, the polynucleotide encodes at least one complete domain of a disorazole polyketide synthase. In one embodiment, the polynucleotide encodes at least one complete ketosynthase, acyl carrier protein, ketoreductase, dehydratase, or acyltransferase domain of disorazole PKS. In a related aspect, a polynucleotide encodes at least one complete module of a disorazole polyketide synthase (selected from the modules 1-8 of disorazole PKS). In a related aspect, a polynucleotide encodes an acyltransferase activity.

[0037] In one aspect, the invention provides a polynucleotide comprising a sequence identical or substantially identical SEQ ID NO: 1 or its complement, or to a portion of SEQ ID NO: 1 or its complement encoding a domain, module, ORF, or region (e.g., as shown in Table 1). (Reference herein to SEQ ID NO:1 will be understood to refer also to the complementary nucleic acid sequence, except where clear from context that reference to a particular strand in intended.) In one aspect, the invention provides a polynucleotide comprising a sequence identical or substantially identical a fragment of SEQ ID NO:1 described in the Examples, *infra*, or a sequencing variant of SEQ ID NO: 1 described in the Examples, or a portion thereof encoding a domain, module, ORF, or region. As used in this context, two nucleic acid sequences (or two polypeptide sequences) are substantially identical if they have at least about 70% sequence identity, often at least about 80%, at least about 90%, at least about 95%, or even at least about 98% sequence identity. A degree of sequence identity can be determined by conventional methods, e.g., Smith and Waterman, 1981, *Adv. Appl. Math.* 2:482, by the search for similarity method of Pearson & Lipman, 1988, *Proc. Natl. Acad. Sci. USA* 85:2444, using the CLUSTAL W algorithm of Thompson et al., 1994, *Nucleic Acids Res* 22:467380, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin

Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI. The BLAST algorithm (Altschul et al., 1990, *Mol. Biol.* 215:403-10) for which software may be obtained through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/) can also be used. When using any of the aforementioned algorithms, the default parameters for "Window" length. gap penalty, etc., are used. It will be appreciated that a reference to a DNA sequence is also a reference to the reverse complement of that sequence (e.g., the sequence of the complementary DNA strand).

[0038] Substantial sequence identity for nucleic acids can also be determined from the ability of the nucleic acids to hybridize with each other (or to the complementary sequence) under stringent hybridization conditions. "Stringent hybridization conditions" refers to conditions in a range from about 5°C to about 20°C or 25°C below the melting temperature (Tm) of the target sequence and a probe with exact or nearly exact complementarity to the target. As used herein, the melting temperature is the temperature at which a population of double-stranded nucleic acid molecules becomes half-dissociated into single strands. Methods for calculating the T_M of nucleic acids are well known in the art (see, e.g., Berger and Kimmel, 1987, Methods In Enzymology, Vol. 152: Guide To Molecular Cloning Techniques, San Diego: Academic Press, Inc. and Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd Ed., Vols. 1-3, Cold Spring Harbor Laboratory). Typically, stringent hybridization conditions are salt concentrations less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion at pH 7.0 to 8.3, and temperatures about 50°C, alternatively about 60°C for probes greater than 50 nucleotides. As noted, stringent conditions may also be achieved with the addition of destabilizing agents such as formamide, in which case lower temperatures may be employed. As noted, stringent conditions may also be achieved with the addition of destabilizing agents such as formamide, in which case lower temperatures may be employed. Exemplary conditions include hybridization at 7% sodium dodecyl sulfate (SDS), 0.5 M $NaPO_4$ pH 7.0, 1 mM EDTA at 50°C (or alternatively 65°C); wash with 2×SSC, 1% SDS, at 50°C (or alternatively 0.1 - 0.2 ×SSC, 1% SDS, at 50°C or 65°C). Other exemplary conditions for hybridization include (1) high stringency: 0.1×SSPE, 0.1% SDS, 65°C.; (2) medium stringency: 0.2×SSPE, 0.1% SDS, 50° C.; and (3) low stringency: 1.0×SSPE, 0.1% SDS, 50° C. Equivalent stringencies may be achieved using alternative buffers, salts and temperatures.

[0039] In an embodiment, a polynucleotide that is substantially identical to a region of SEQ ID NO:1 encodes a polypeptide with a biological activity (e.g., enzymatic activity) of the corresponding region of SEQ ID NO:1 (e.g., the enzymatic activity of a KS, AT, ACP, DH, KR, MT, Cy, TE, ACP, A, PCP, or Ox domain of a disorazole PKS).

[0040] In a related aspect, the invention provides a recombinant DNA molecule, comprising a sequence of at least about 200, optionally at least about 500, basepairs with a sequence identical or substantially identical to a protein encoding region of *dszA*, *dszB*, *dszC* or *dsz*D. In an embodiment, the DNA molecule encodes a polypeptide, module or domain derived from a disorazole polyketide synthase (PKS) gene cluster.

[0041] The invention provides polypeptides comprising a sequence encoded by a polynucleotide disclosed herein. In an embodiment, the invention provides a recombinant protein comprising a module (e.g., a loading module, an acetyltransferase (AT) module, or module 1, 2, 3, 4, 5, 6, 7 or 8 of the disorazole PKS) or domain (e.g., KS, AT, ACP, DH, KR) of disorazole PKS. In one embodiment, the invention provides a recombinant PKS that produces a disorazole when expressed in a suitable cell (e.g., as described hereinbelow).

[0042] In one embodiment, the invention provides polynucleotides comprising at least about 12, 15, 25, 50, 75, 100, 500, or 1000 contiguous nucleotides as set forth in SEQ ID NO: 1, or a fragment thereof, or sequencing variant thereof. In an embodiment, the polynucleotide encodes a polypeptide with the biological activity (e.g., enzymatic activity) of the corresponding region of SEQ ID NO:1. In a related embodiment, the invention provides polynucleotides that encode a polypeptide that comprises at least 10, 15, 20, 30 or more contiguous amino acids encoded by SEQ ID NO: 1. Those of skill will recognize that, due to the degeneracy of the genetic code, a large number of DNA sequences encode the amino acid sequences of the domains, modules, and proteins of the disorazole PKS, the enzymes involved in disorazole modification and other polypeptides encoded by the genes of the disorazole biosynthetic gene cluster and flanking region. The present invention contemplates all such DNAs. For example, it may be advantageous to optimize sequence to account for the codon preference of a host organism. The invention also contemplates naturally occurring genes encoding the disorazole PKS and tailoring enzymes that are polymorphic or other variants. In addition, it will be appreciated that polypeptide, modules and domains of the invention may comprise one or more conservative amino acid substitutions relative to the polypeptides encoded by SEQ ID NO:1. A conservative

substitution is one that does not destroy the biological activity of the polypeptide, domain, or region; for example, conservative substitutions include aspartic-glutamic as acidic amino acids; lysine/arginine/histidine as basic amino acids; leucine/isoleucine, methionine/valine, alanine/valine as hydrophobic amino acids; serine/glycine/alanine/threonine as hydrophilic amino acids.

[0043] As used herein the term "recombinant" has its usual meaning in the art and refers to a polynucleotide synthesized or otherwise manipulated *in vitro*, or to methods of using recombinant polynucleotides to produce gene products in cells or other biological systems. Thus, a "recombinant" polynucleotide is defined either by its method of production or its structure. In reference to its method of production, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence, typically selection or production. Alternatively, a recombinant polynucleotide can be a polynucleotide made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature. Thus, for example, products made by transforming cells with any non-naturally occurring vector is encompassed, as are polynucleotides comprising sequence derived using any synthetic oligonucleotide process, as are polynucleotides from which a region has been deleted. A recombinant polynucleotide can also be a coding sequence that has been modified *in vivo* using a recombinant oligo or polynucleotide (such as a PKS in which a domain is inactivated by homologous recombination using a recombinant polynucleotide). A "recombinant" polypeptide is one expressed from a recombinant polynucleotide.

[0044] The recombinant nucleic acids of the invention have a variety of uses, including use (1) for the synthesis of polyketides such as disorazoles and disorazole derivatives, (2) for production of chimeric and hybrid PKS proteins, which can be used for biosynthesis of novel polyketides, (3) for the generation of mutants of disorazole PKS proteins and domains, (4) in the design and synthesis of probes or primers for detection and manipulation of PKS genes and for amplification and analysis of PKS gene sequences, (5) for design and synthesis of peptides or polypeptides for generation of antibodies (e.g., for immunopurification of PKS proteins), (6) for preparation of vectors useful to knock-out an activity encoded by the disorazole PKS gene cluster (7) preparation of vectors useful for PKS domain substitutions or modification and (8) for other uses apparent to the ordinarily-skilled practitioner reading the present disclosure.

[0045] In one aspect of the invention, the PKS-domain encoding polynucleotides of the invention are operably linked to expression control sequences (e.g., promoter sequences) so that expression in host cells is effective. In an embodiment the control sequences are the same, or essentially the same, as those operably linked in the *S. cellulosum* (So ce12 strain) genome with the disorazole PKS sequences.

[0046] As noted, the present invention also provides polypeptides encoded by the above-described polynucleotides. Methods for conceptual translation and analysis of nucleotide sequences are well known, and those of skill reading this disclosure will be apprised of the sequence and characteristics of polypeptides encoded by the polynucleotides of the invention.

[0047] In an embodiment, the invention provides a polypeptide comprising at least 10, 15, 20, or more contiguous amino acids encoded by a polynucleotide described hereinabove. The invention also provides amino acid sequences that differ from the proteins of the disorazole PKS by insubstantial changes to the amino acid composition, *i.e.*, by amino acid substitutions, but perform the same biosynthetic functions as the proteins herein disclosed.

[0048] In one aspect, the invention provides an isolated or recombinant DNA molecule comprising a nucleotide sequence that encodes at least one polypeptide, module or domain encoded by *dszA*, *dszB*, *dszC* or the disorazole PKS AT domain gene (*dsz*D), e.g., a polypeptide, module or domain involved in the biosynthesis of a disorazole, wherein said nucleotide sequence comprises at least 20, 25, 30, 35, 40, 45, or 50 contiguous base pairs identical or substantially identical to *dszA*, *dszB*, *dszC* or *dsz*D. In one aspect, the invention provides an isolated or recombinant DNA molecule comprising a nucleotide sequence that encodes at least one polypeptide, module or domain involved in the biosynthesis of a disorazole, wherein said polypeptide, module or domain comprises at least 10, 15, 20, 30, or 40 contiguous residues of a corresponding polypeptide, module or domain encoded by *dszA*, *dszB*, *dszC* or *dsz*D.

[0049] The invention also provides cells comprising recombinant DNA molecules and vectors comprising recombinant DNA molecules that encode all or a portion of the disorazole PKS and are operably linked to expression control sequences that are effective in a suitable host cell. When such DNA molecules are introduced into a host cell and the host cell is cultured under conditions that lead to the expression of disorazole PKS proteins, disorazole and and/or its analogs or derivatives may be produced. In one embodiment, the expression control sequences

are those normally associated with a module of the *Sorangium cellulosum* disorazole polyketide synthase gene cluster.

[0050] In related embodiments, the invention provides a recombinant vector encoding a disorazole AT domain; (2) a cell in which a disorazole AT domain is modified or inactive; (3) a chimeric PKS comprising a disorazole PKS AT domain. In related embodiments, the invention provides a recombinant vector encoding (1) a recombinant vector encoding a disorazole *dsz*A gene; (2) a cell in which a disorazole *dsz*A gene is modified or inactive; (3) a chimeric PKS comprising a domain encoded by the *dsz*A gene. In related embodiments, the invention provides (1) a recombinant vector encoding a disorazole *dsz*B gene; (2) a cell in which a disorazole *dsz*B gene is modified or inactive; (3) a chimeric PKS comprising a domain encoded by the *dsz*B gene. In related embodiments, the invention provides (1) a recombinant vector encoding a disorazole *dsz*C gene; (2) a cell in which a disorazole *dsz*C gene is modified or inactive; (3) a chimeric PKS comprising a domain encoded by the *dsz*C gene. In related embodiments, the invention provides (1) a recombinant vector encoding a disorazole *dsz*D gene; (2) a cell in which a disorazole *dsz*D gene is modified or inactive; (3) a chimeric PKS comprising a domain encoded by the *dsz*D gene. In one embodiment, the invention provides a recombinant *Sorangium cellulosum* cell in which a *dsz*A, *dsz*B, *dsz*C, or *dsz*D gene is disrupted so as to reduce or eliminate production of disorazole. Guided by the present disclosure (including the sequence of the disorazole PKS genes) such disruption, or knockout, can be accomplished using routine methods.

[0051] In other related aspects, the invention provides (1) a PKS derived from the disorazole PKS by inactivation, addition or rearrangement of disorazole PKS domains or modules, and recombinant DNA molecules and vectors encoding such derivative PKSs; (2) chimeric or hybrid PKSs and recombinant DNA molecules and vectors encoding such chimeric or hybrid PKSs; and (3) PKS libraries comprising disorazole PKS domains. It will be understood by the reader that expression of such derivatives, hybrids, or libraries can be implemented in the same fashion (e.g., same hosts, control sequences, etc.) as is described in connection with production of disorazole PKSs.

[0052] It will be recognized by those of skill that recombinant polypeptides of the invention have a variety of uses, some of which are described in detail below, including but not limited to use as enzymes, or components of enzymes, useful for the synthesis or modification of

polyketides. Recombinant polypeptides encoded by the disorazole PKS gene cluster are also useful as antigens for production of antibodies. Such antibodies find use for purification of bacterial (e.g., *Sorangium cellulosum*) proteins, detection and typing of bacteria, and particularly, as tools for strain improvement (e.g., to assay PKS protein levels to identify "up-regulated" strains in which levels of polyketide producing or modifying proteins are elevated) or assessment of efficiency of expression of recombinant proteins. Polyclonal and monoclonal antibodies can be made by well known and routine methods (see, e.g., Harlow and Lane, 1988, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York; Koehler and Milstein 1075, Nature 256:495). In selecting polypeptide sequences for antibody production, it is not necessary to retain biological activity; however, the protein fragment must be immunogenic, and preferably antigenic (as can be determined by routine methods). Generally the protein fragment is produced by recombinant expression of a DNA comprising at least about 60, more often at least about 200, or even at least about 500 or more base pairs of protein coding sequence, such as a polypeptide, module or domain derived from a disorazole polyketide synthase (PKS) gene cluster. Methods for expression of recombinant proteins are well known. (See, e.g., Ausubel et al., 2002, Current Protocols In Molecular Biology, Greene Publishing and Wiley-Interscience, New York.)

Disorazole PKS Derivatives

[0053] In one aspect, the invention provides recombinant DNA molecules (and vectors comprising those recombinant DNA molecules) that encode all or a portion of the disorazole PKS and which, when transformed into a host cell and the host cell is cultured under conditions that lead to the expression of the disorazole PKS proteins and results in the production of disorazole, disorazole analogs or disorazole derivatives. In an embodiment, these recombinant DNA molecules can differ from a naturally occurring disorazole PKS gene cluster due to a mutation in a disorazole PKS domain-encoding sequence, resulting in deletion or inactivation of a PKS domain, or, alternatively, addition of a sequence encoding a domain of a disorazole or heterologous PKS domain to the disorazole PKS gene cluster, resulting in rearrangements of domains or modules of the disorazole PKS, or alternatively, gene modifications resulting in deletion or addition of a polyketide modifying enzyme (e.g., a methyltransferase, an oxidase or a glycosylation enzyme). It will be understood from this that the invention provides methods of making analogs of disorazole compounds by modifying the activity of the domains of the

disorazole PKS. As noted above, modification of the domains of the disorazole PKS can be effected by, among other methods, deletion of the complete or partial coding sequence for a given domain resulting in inactivation of the domain, or by site-directed mutagenesis or point mutation that results in altered activity of the domains, and/or by addition or rearrangement of domains.

[0054] Mutations can be made to the native disorazole PKS sequences using any number of conventional techniques. The substrates for mutation can be an entire cluster of genes or only one or two of them; the substrate for mutation may also be portions of one or more of these genes. Techniques for mutation include preparing synthetic oligonucleotides including the mutations and inserting the mutated sequence into the gene encoding a PKS subunit using restriction endonuclease digestion (see, *e.g.*, Kunkel, 1985, *Proc Natl Acad Sci USA* 82:448; and Geisselsoder *et al.*, 1987, *BioTechniques* 5:786). Alternatively, the mutations can be effected using a mismatched primer (generally 10-20 nucleotides in length) which hybridizes to the native nucleotide sequence (generally cDNA corresponding to the RNA sequence) at a temperature below the melting temperature of the mismatched duplex. The primer can be made specific by keeping primer length and base composition within relatively narrow limits and by keeping the mutant base centrally located (see Zoller and Smith, 1983, *Methods in Enzymology* 100:468). Primer extension is effected using DNA polymerase. The product of the extension reaction is cloned, and those clones containing the mutated DNA are selected. Selection can be accomplished using the mutant primer as a hybridization probe. The technique is also applicable for generating multiple point mutations (see, *e.g.*, Dalbie-McFarland *et al.* 1982, *Proc Natl Acad Sci USA* 79:6409). PCR mutagenesis can also be used for effecting the desired mutations. Many other suitable methods for manipulating PKS encoding sequences will be apparent.

[0055] In a related aspect, the invention provides a PKS derived from the disorazole PKS. A polyketide synthase may be considered "derived from" a naturally occurring PKS (e.g., disorazole) when it contains the scaffolding encoded by all the portion employed of the naturally occurring synthase gene, contains at least two modules that are functional, and contains mutations, deletions, or replacements of one or more of the activities of these functional modules so that the nature of the resulting polyketide is altered. Particular embodiments include those wherein a KS, AT, KR, DH, NRPS, or ER has been deleted or replaced by a version of the activity from a different PKS or from another location within the same PKS. Also contemplated

are derivatives where at least one noncondensation cycle enzymatic activity (KR, DH, or ER) has been deleted or where any of these activities has been mutated so as to change the ultimate polyketide synthesized. Regions encoding corresponding activities from different PKS synthases or from different locations in the same PKS synthase can be recovered, for example, using PCR techniques with appropriate primers. (By "corresponding" activity encoding regions is meant those regions encoding the same general type of activity, e.g., a ketoreductase activity in one location of a gene cluster would "correspond" to a ketoreductase-encoding activity in another location in the gene cluster or in a different gene cluster.)

[0056] If replacement of a particular target region in a host polyketide synthase is to be made, this replacement can be conducted *in vitro* using suitable restriction enzymes or can be effected *in vivo* using recombinant techniques involving homologous sequences framing the replacement gene. One such system involving plasmids of differing temperature sensitivities are described in PCT application WO 96/40968. Another useful method for modifying a PKS gene (e.g., making domain substitutions or "swaps") is a RED/ET cloning procedure developed for constructing domain swaps or modifications in an expression plasmid without first introducing restriction sites. The method is related to ET cloning methods (see, Datansko & Wanner, 2000, Proc. Natl. Acad. Sci. U.S.A. 97, 6640-45; Muyrers et al, 2000, Genetic Engineering 22:77-98). The RED/ET cloning procedure is used to introduce a unique restriction site in the recipient plasmid at the location of the targeted domain. This restriction site is used to subsequently linearize the recipient plasmid in a subsequent ET cloning step to introduce the modification. This linearization step is necessary in the absence of a selectable marker, which cannot be used for domain substitutions. An advantage of using this method for PKS engineering is that restriction sites do not have to be introduced in the recipient plasmid in order to construct the swap, which makes it faster and more powerful because boundary junctions can be altered more easily.

PKS Libraries

[0057] The disorazole PKS-encoding polynucleotides of the invention may also be used in the production of libraries of PKSs. The invention provides libraries of polyketides by generating modifications in, or using a portion of, the disorazole PKS so that the protein complexes produced by the cluster have altered activities in one or more respects, and thus

produce polyketides other than the natural disorazole product of the PKS. Novel polyketides may thus be prepared, or polyketides in general prepared more readily, using this method. By providing a large number of different genes or gene clusters derived from a naturally occurring PKS gene cluster, each of which has been modified in a different way from the native PKS cluster, an effectively combinatorial library of polyketides can be produced as a result of the multiple variations in these activities. Expression vectors containing nucleotide sequences encoding a variety of PKS systems for the production of different polyketides can be transformed into the appropriate host cells to construct a polyketide library. In one approach, a mixture of such vectors is transformed into the selected host cells and the resulting cells plated into individual colonies and selected for successful transformants. Each individual colony has the ability to produce a particular PKS synthase and ultimately a particular polyketide. A variety of strategies can be devised to obtain a multiplicity of colonies each containing a PKS gene cluster derived from the naturally occurring host gene cluster so that each colony in the library produces a different PKS and ultimately a different polyketide. The number of different polyketides that are produced by the library is typically at least four, more typically at least ten, and preferably at least 20, more preferably at least 50, reflecting similar numbers of different altered PKS gene clusters and PKS gene products. The number of members in the library is arbitrarily chosen; however, the degrees of freedom outlined above with respect to the variation of starter, extender units, stereochemistry, oxidation state, and chain length is quite large. The polyketide producing colonies can be identified and isolated using known techniques and the produced polyketides further characterized. The polyketides produced by these colonies can be used collectively in a panel to represent a library or may be assessed individually for activity.

[0058] Colonies in the library are induced to produce the relevant synthases and thus to produce the relevant polyketides to obtain a library of candidate polyketides. The polyketides secreted into the media can be screened for binding to desired targets, such as receptors, signaling proteins, and the like. The supernatants *per se* can be used for screening, or partial or complete purification of the polyketides can first be effected. Typically, such screening methods involve detecting the binding of each member of the library to receptor or other target ligand. Binding can be detected either directly or through a competition assay. Means to screen such libraries for binding are well known in the art. Alternatively, individual polyketide members of

the library can be tested against a desired target. In this event, screens wherein the biological response of the target is measured can be included.

Chimeric PKSs

[0059] In a further aspect, the invention provides methods for expressing chimeric or hybrid PKS encoding polynucleotides and products of such PKSs. As used herein, "chimeric" and "hybrid" are used interchangeably and include both (1) fusion proteins comprising regions encoded by the Disorazole PKS sequence and regions encoded by non-Disorazole PKS sequence and (2) PKS multiprotein complexes comprising polypeptide(s) encoded by *dsz*A, B, C or D and polypeptides from non-Disorazole PKS(s). For example, the invention provides (1) encoding DNA for a chimeric PKS that is substantially patterned on a non-disorazole producing enzyme, but which includes one or more functional domains or modules of disorazole PKS; (2) encoding DNA for a chimeric PKS that is substantially patterned on the disorazole PKS, but which includes one or more functional domains or modules of another PKS or NRPS; and (3) methods for making disorazole analogs and derivatives.

[0060] With respect to item (1) above, in one embodiment, the invention provides chimeric PKS enzymes in which the genes for a non-disorazole PKS (e.g., the erythromycin PKS, epothilone PKS, rapamycin PKS) function as accepting genes, and one or more of the above-identified coding sequences for disorazole domains or modules are inserted as replacements for one or more domains or modules of comparable function. There are a wide variety of PKS genes that serve as readily available sources of DNA and sequence information for use in constructing the hybrid PKS-encoding DNA compounds of the invention. Methods for constructing hybrid PKS-encoding DNA compounds are described in U.S. Patent Nos. 5,672,491; 5,712,146; and 6509455. A partial list of sources of PKS sequences for use in making chimeric molecules, for illustration and not limitation, includes Avermectin (U.S. Pat. No. 5,252,474; MacNeil et al., 1993, Industrial Microorganisms: Basic and Applied Molecular Genetics, Baltz, Hegeman, & Skatrud, eds. (ASM), pp. 245-256; MacNeil et al., 1992, Gene 115: 119-25); Candicidin (FRO008) (Hu et al., 1994, *Mol. Microbiol.* 14: 163-72); Epothilone (U.S. Pat. No. 6,303,342); Erythromycin (WO 93/13663; U.S. Pat. No. 5,824,513; Donadio et al., 1991, *Science* 252:675-79; Cortes et al., 1990, *Nature* 348:176-8); FK-506 (Motamedi et al., 1998, *Eur. J. Biochem.* 256:528-34; Motamedi et al., 1997, *Eur. J. Biochem.* 244:74-80); FK-520 (U.S. Pat. No.

6,503,737; see also Nielsen et al., 1991, *Biochem.* 30:5789-96); Lovastatin (U.S. Pat. No. 5,744,350); Nemadectin (MacNeil et al., 1993, *supra*); Niddamycin (Kakavas et al., 1997, *J. Bacteriol.* 179:7515-22); Oleandomycin (Swan et al., 1994, *Mol. Gen. Genet.* 242:358-62; U.S. Pat. No. 6,388,099; Olano et al., 1998, *Mol. Gen. Genet.* 259:299-308); Platenolide (EP Pat. App. 791,656); Rapamycin (Schwecke et al., 1995, *Proc. Natl. Acad. Sci. USA* 92:7839-43); Aparicio et al., 1996, *Gene* 169:9-16); Rifamycin (August et al., 1998, *Chemistry & Biology*, 5: 69-79); Soraphen (U.S. Pat. No. 5,716,849; Schupp et al., 1995, *J. Bacteriology* 177: 3673-79); Spiramycin (U.S. Pat. No. 5,098,837); Tylosin (EP 0 791,655; Kuhstoss et al., 1996, Gene 183:231-36; U.S. Pat. No. 5,876,991). Additional suitable PKS coding sequences remain to be discovered and characterized, but will be available to those of skill (e.g., by reference to GenBank).

[0061] As noted, construction of such enzymes is most effectively achieved by construction of appropriate encoding polynucleotides. In this example of the invention, it is not necessary to replace an entire domain or module accepting of the PKS with an entire domain or module of disorazole PKS, rather peptide subsequences of a PKS domain or module that correspond to a peptide subsequence in an accepting domain or module, or which otherwise provide useful function, may be used as replacements. Accordingly, appropriate encoding DNAs for construction of such chimeric PKS include those that encode at least 10, 15, 20 or more amino acids of a selected disorazole domain or module.

[0062] The use of the appropriate interpolypeptide linkers directs the proper assembly of the PKS, thereby improving the catalytic activity of the resulting hybrid PKS. In one embodiment, the components of a chimeric PKS are arranged onto polypeptides having interpolypeptide linkers that direct the assembly of the polypeptides into the functional PKS protein, such that it is not required that the PKS have the same arrangement of modules in the polypeptides as observed in natural PKSs. Suitable interpolypeptide linkers to join polypeptides and intrapolypeptide linkers to join modules within a polypeptide are described in PCT publication WO 00/47724.

Expression

[0063] The present invention provides recombinant DNA molecules and vectors comprising recombinant DNA molecules that encode all or a portion of the disorazole PKS and/or disorazole modification enzymes and that, when transformed into a host cell and the host cell is cultured

under conditions that lead to the expression of said disorazole PKS and/or modification enzymes, results in the production of polyketides including but not limited to disorazole and/or analogs or derivatives thereof in useful quantities. The present invention also provides recombinant host cells comprising those recombinant vectors.

[0064] The DNA compounds of the invention can be expressed in host cells for production of known and novel compounds. A variety of hosts may be used for expression of disorazole PKS proteins. The various PKS nucleotide sequences, or a mixture of such sequences, can be cloned into one or more recombinant vectors as individual cassettes, with separate control elements or under the control of a single promoter. The encoding sequence for PKS subunits or components can include flanking restriction sites to allow for the easy deletion and insertion of other PKS subunits so that hybrid or chimeric PKSs can be generated. The design of such restriction sites is known to those of skill in the art and can be accomplished using the techniques described above, such as site-directed mutagenesis and PCR. Methods for introducing the recombinant vectors of the present invention into suitable hosts are known to those of skill in the art and typically include electroporation, conjugation, protoplast transformation, or the use of agents such as $CaCl_2$, lipofection, DMSO. Selectable markers can also be included in the recombinant expression vectors. A variety of markers are known which are useful in selecting for transformed cell lines and generally comprise a gene whose expression confers a selectable phenotype on transformed cells when the cells are grown in an appropriate selective medium. Such markers include, for example, genes which confer antibiotic resistance or sensitivity. In one embodiment the exogenous DNA sequence is integrated into the chromosomal DNA of the host cell.

[0065] Preferred hosts include fungal systems such as yeast and procaryotic hosts (e.g., *Streptomyces*, *E. coli*), Single cell cultures of mammalian cells can also be used. A variety of methods for heterologous expression of PKS genes and host cells suitable for expression of these genes and production of polyketides are described, for example, in U.S. Patent Nos. 5,843,718 and 5,830,750; WO 01/31035, WO 01/27306, and WO 02/068613; and U.S. patent application nos. 10/087,451 (published as US2002000087451); 60/355,211; and 60/396,513 (corresponding to published application 20020045220).

[0066] A particularly useful host cell is of genus *Myxococcus*, e.g., *Myxococcus xanthus*, the use of which is described in U.S. Patent No. 6,410,301. In this respect, the inventors have

discovered that *Sorangium cellulosum* expression control sequences (e.g., promoters) associated with polyketide synthase genes also drive transcription in *Myxococcus xanthus* host cells and it is expected that the disorazole PKS control sequences will function in *Myxococcus*. Accordingly, the *S. cellulosum* disorazole PKS control sequences are conveniently used for heterologous expression in *M. xanthus*.

[0067] As disclosed in U.S. Patent No. 6,033,883 a wide variety of hosts can be used, even though some hosts natively do not contain the appropriate post-translational mechanisms to activate the acyl carrier proteins of the synthases. These hosts can be modified with the appropriate recombinant enzymes to effect these modifications. In one embodiment, the host lacks its own means for producing polyketides so that a more homogeneous product is obtained. In one embodiment, native modular PKS genes in the host cell have been deleted to produce a "clean host," as described in US Patent 5,672,491.

[0068] Appropriate host cells for the expression of PKS genes (including hybrid PKS) genes include those organisms capable of producing the needed precursors, such as malonyl-CoA, methylmalonyl-CoA, ethylmalonyl-CoA, and methoxymalonyl-ACP, and having phosphopantotheinylation systems capable of activating the ACP domains of modular PKSs. See, for example, US Patent 6,579,695. However, as disclosed in U.S. Patent No. 6,033,883, a wide variety of hosts can be used, even though some hosts natively do not contain the appropriate post-translational mechanisms to activate the acyl carrier proteins of the synthases. Also see WO 97/13845 and WO 98/27203. The host cell may natively produce none, some, or all of the required polyketide precursors, and may be genetically engineered so as to produce the required polyketide precursors. Such hosts can be modified with the appropriate recombinant enzymes to effect these modifications. Suitable host cells include *Streptomyces*, *E. coli*, yeast, and other procaryotic hosts which use control sequences compatible with *Streptomyces spp.* Examples of suitable hosts that either natively produce modular polyketides or have been engineered so as to produce modular polyketides include but are not limited to actinomycetes such as *Streptomyces coelicolor, Streptomyces venezuelae, Streptomyces fradiae, Streptomyces ambofaciens,* and *Saccharopolyspora erythraea,* eubacteria such as *Escherichia coli,* myxobacteria such as *Myxococcus xanthus*, and yeasts such as *Saccharomyces cerevisiae.* In one embodiment, any native modular PKS genes in the host cell have been deleted or inactivated to produce a "clean host" (see US Patent 5,672,491).In some embodiments, the host cell

expresses, or is engineered to express, a polyketide "tailoring" or "modifying" enzyme. Once a PKS product is released, it is subject to post-PKS tailoring reactions. These reactions are important for biological activity and for the diversity seen among macrolides. Tailoring enzymes normally associated with polyketide biosynthesis include oxygenases, glycosyl- and methyltransferases, acyltransferases, halogenases, cyclases, aminotransferases, and hydroxylases. Tailoring enzymes for modification of a product of the disorazole PKS, a non-disorazole PKS, or a chimeric PKS, can be those normally associated with disorazole biosynthesis or "heterologous" tailoring enzymes.

[0069] For purposes of the present invention, tailoring enzymes can be expressed in the organism in which they are naturally produced, or as recombinant proteins in heterologous hosts. In some cases, the structure produced by the heterologous or hybrid PKS may be modified with different efficiencies by post-PKS tailoring enzymes from different sources. In such cases, post-PKS tailoring enzymes can be recruited from other pathways to obtain the desired compound. Similarly, host cells can be selected, or engineered, for expression of a glycosylatation apparatus, amide synthases, (see, for example, U.S. patent publication 20020045220 "Biosynthesis of Polyketide Synthase Substrates"). For example and not limitation, the host cell can contain the desosamine, megosamine, and/or mycarose biosynthetic genes, corresponding glycosyl transferase genes, and hydroxylase genes (e.g., picK, megK, eryK, megF, and/or eryF). Methods for glycosylating polyketides are generally known in the art and can be applied in accordance with the methods of the present invention; the glycosylation may be effected intracellularly by providing the appropriate glycosylation enzymes or may be effected *in vitro* using chemical synthetic means as described herein and in PCT publication WO 98/49315. Glycosylation with desosamine, mycarose, and/or megosamine is effected in accordance with the methods of the invention in recombinant host cells provided by the invention. Alternatively and as noted, glycosylation may be effected intracellularly using endogenous or recombinantly produced intracellular glycosylases. In addition, synthetic chemical methods may be employed.

[0070] Alternatively, the aglycone compounds can be produced in the recombinant host cell, and the desired modification (e.g., glycosylation and hydroxylation) steps carried out *in vitro* (e.g., using purified enzymes, isolated from native sources or recombinantly produced) or *in vivo* in a converting cell different from the host cell (e.g., by supplying the converting cell with the aglycone).

[0071] Suitable control sequences for gene expression in various types of organisms are well known in the art. Control systems for expression in yeast are widely available and are routinely used. Control elements include promoters, optionally containing operator sequences, and other elements (such as ribosome binding sites) depending on the nature of the host. Particularly useful promoters for procaryotic hosts include those from PKS gene clusters which result in the production of polyketides as secondary metabolites, including those from Type I or aromatic (Type II) PKS gene clusters. Examples are *act* promoters, *tcm* promoters, spiramycin promoters, and the like. However, other bacterial promoters, such as those derived from sugar metabolizing enzymes, such as galactose, lactose (*lac*) and maltose, are also useful. Additional examples include promoters derived from biosynthetic enzymes such as for tryptophan (*trp*), the β-lactamase (*bla*), bacteriophage lambda PL, and T7. In addition, synthetic promoters, such as the *tac* promoter can be used. Illustrative control sequences, vectors, and host cells of these types include the modified *S. coelicolor* CH999 and vectors described in PCT publication WO 96/40968 and similar strains of *S. lividans*. See U.S. Patent Nos. 4,551,433, 5,672,491; 5,830,750, 5,843,718; and 6,177,262. The recombinant host cell can be cultured under conditions where a polyketide is produced by biosynthetic acitivity of a synthase comprising a protein comprising at least one domain (usually at least one module, or at least one polypeptide) encoded by a polynucleotide of the invention.

[0072] As discussed above, the sequenced region of the disorazole PKS gene cluster does not including a conventional loading module. If a separate loading module is used by *Sorangium cellulosum*, such that expression of *dszA*, *dszB*, *dszC*, and *dszD* would not result in the synthesis of disorazole if expressed in a heterologous host, such as *M. xanthus*, "SNAC feeding" can be used in the synthesis of polyketides (Jacobsen et al., 1997 "Precursor-directed biosynthesis of erythromycin analogs by an engineered polyketide synthase" *Science* 277:367-369). Alternatively, a recombinant loading module (e.g., from *Sorangium*) can be introduced into the cell or other methods for loading can be used.

[0073] Suitable culture conditions for production of polyketides using the cells of the invention will vary according to the host cell and the nature of the polyketide being produced, but will be know to those of skill in the art. See, for example, WO 98/27203 "Production of Polyketides in Bacteria and Yeast" and WO 01/83803 "Overproduction Hosts for Biosynthesis of Polyketides."

[0074] The polyketide product produced by host cells of the invention can be recovered (*i.e.*, separated from the producing cells and at least partially purified) using routine techniques (e.g., extraction from broth followed by chromatography).

[0075] The compositions, cells and methods of the invention may be directed to the preparation of an individual polyketide or a number of polyketides. The polyketide may or may not be novel, but the method of preparation permits a more convenient or alternative method of preparing it. It will be understood that the resulting polyketides may be further modified to convert them to other useful compounds. For example, an ester linkage may be added to produce a "pharmaceutically acceptable ester" (i.e., an ester that hydrolyzes under physiologically relevant conditions to produce a compound or a salt thereof). Illustrative examples of suitable ester groups include but are not limited to formates, acetates, propionates, butyrates, succinates, and ethylsuccinates.

[0076] The polyketide product produced by recombinant cells can be chemically modified in a variety of ways (for example, a protecting group can be added to produce prodrug forms or for other purposes). A variety of protecting groups are disclosed, for example, in T.H. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, New York (1999). Prodrugs are in general functional derivatives of the compounds that are readily convertible *in vivo* into the required compound. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," H. Bundgaard ed., Elsevier, 1985.

[0077] Similarly, improvements in water solubility of a polyketide compound can be achieved by addition of groups containing solubilizing functionalities to the compound or by removal of hydrophobic groups from the compound, so as to decrease the lipophilicity of the compound. Typical groups containing solubilizing functionalities include, but are not limited to: 2-(dimethylaminoethyl)amino, piperidinyl, N-alkylpiperidinyl, hexahydropyranyl, furfuryl, tetrahydrofurfuryl, pyrrolidinyl, N-alkylpyrrolidinyl, piperazinylamino, N-alkylpiperazinyl, morpholinyl, N-alkylaziridinylmethyl, (1-azabicyclo[1.3.0]hex-1-yl)ethyl, 2-(N-methylpyrrolidin-2-yl)ethyl, 2-(4-imidazolyl)ethyl, 2-(1-methyl-4-imidazolyl)ethyl, 2-(1-methyl-5-imidazolyl)ethyl, 2-(4-pyridyl)ethyl, and 3-(4-morpholino)-1-propyl.

[0078] In addition to post synthesis chemical or biosynthetic modifications, various polyketide forms or compositions can be produced, including but not limited to mixtures of

polyketides, enantiomers, diastereomers, geometrical isomers, polymorphic crystalline forms and solvates, and combinations and mixtures thereof can be produced

[0079] Many other modifications of polyketides produced according to the invention will be apparent to those of skill, and can be accomplished using techniques of pharmaceutical chemistry.

[0080] Prior to use the PKS product (whether modified or not) can be formulated for storage, stability or administration. For example, the polyketide products can be formulated as a "pharmaceutically acceptable salt." Suitable pharmaceutically acceptable salts of compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, benzoic acid, acetic acid, citric acid, tartaric acid, phosphoric acid, carbonic acid, or the like. Where the compounds carry one or more acidic moieties, pharmaceutically acceptable salts may be formed by treatment of a solution of the compound with a solution of a pharmaceutically acceptable base, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, tetraalkylammonium hydroxide, lithium carbonate, sodium carbonate, potassium carbonate, ammonia, alkylamines, or the like.

[0081] Prior to administration to a mammal the PKS product will be formulated as a pharmaceutical composition according to methods well known in the art, e.g., combination with a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" refers to a medium that is used to prepare a desired dosage form of a compound. A pharmaceutically acceptable carrier can include one or more solvents, diluents, or other liquid vehicles; dispersion or suspension aids; surface active agents; isotonic agents; thickening or emulsifying agents; preservatives; solid binders; lubricants; and the like. Remington's Pharmaceutical Sciences, Fifteenth Edition, E.W. Martin (Mack Publishing Co., Easton, PA, 1975) and Handbook of Pharmaceutical Excipients, Third Edition, A.H. Kibbe ed. (American Pharmaceutical Assoc. 2000), disclose various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof.

[0082] The composition may be administered in any suitable form such as solid, semisolid, or liquid form. See Pharmaceutical Dosage Forms and Drug Delivery Systems, 5th edition, Lippicott Williams & Wilkins (1991). In an embodiment, for illustration and not limitation, the polyketide is combined in admixture with an organic or inorganic carrier or excipient suitable for

external, internal, or parenteral application. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, pessaries, solutions, emulsions, suspensions, and any other form suitable for use. The carriers that can be used include water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, and other carriers suitable for use in manufacturing preparations, in solid, semi-solid, or liquified form. In addition, auxiliary stabilizing, thickening, and coloring agents and perfumes may be used.

EXAMPLES

EXAMPLE 1

CLONING AND CHARACTERIZATION OF *SORANGIUM CELLULOSUM* DISORAZOLE POLYKETIDE SYNTHASE GENE CLUSTER

[0083] This example describes the cloning of the disorazole PKS gene cluster using a knock-out approach. The strategy described in this example complements a related cloning effort described in U.S. provisional patent application no. 60/431,272, filed December 6, 2002, and incorporated herein in its entirety.

I. Generating transposon insertions in *Sorangium cellulosum* So ce12

[0084] *Sorangium cellulosum* So ce12 was grown in SF medium to an OD_{600} of 1.0. 10 ml of the culture was centrifuged to pellet the cells, and the cells were resuspended in approximately 0.5 ml of the same medium. The composition of SF medium is shown in Table 2.

[0085] The *E. coli* strain harboring the transposon (DH10B, pKOS111-47, pGZ119EH, pKOS249-52 (Phleomycin resistance) or pKOS249-123 (hygromycin resistance) was grown in 10 ml of LB incubated at 37°C overnight without shaking. The overnight *E. coli* culture was centrifuged and the pelleted cells were mixed with the 0.5 ml of concentrated So ce12 cells. The mixed cells were spotted onto the center of an S42 plate and incubated at 30°C overnight. The next day, the cells were scraped from the plates, resuspended in the fructose medium, and aliquots were plated in top agar on S42 plates containing kanamycin (100 μg/ml) and

phleomycin (50 μg/ml) or hygromycin (100 μg/ml). The plates were incubated at 32°C for 7-10 days.

II. Screening For Insertion Strains

[0086] Colonies that appeared on the plates were picked and inoculated into 2 x 96 well microtiter plates contain S42 agar medium. Of the two plates, one had a removable low protein-binding Nylon 66 membrane sealing the bottom (96 MicroWell™ plate with Low Protein Binding Nylon 66 Membrane, Loprodyne™ 1.2 um). Once the colonies had grown up on the "membrane bottom plate," the membrane was removed and the agar plugs containing the growing colonies were pushed into test tubes containing 4 ml of production media containing 2% cyclodextrin.

[0087] The cultures were grown at 30°C for 14 days with shaking. A 1 ml aliquot of the supernatant was filtered through a 96-well glass fiber filter plate and a C18 column (96-well plate). 250 μl of 100% methanol was used to elute from the C18 column. To detect the presence of disorazole in the methanol eluted samples, 20 μl of the methanol extract was subjected to HPLC analysis using a Metachem Inertsil ODS-3 (5μm; 4.6 X 150 mm) column and a linear gradient of 50-100 % MeCN (0.1% HOAc) at 1 mL/min over 8 minutes. The retention time of the disorazole A peak is 8.3 min and has a characteristic UV maximum at 275 nm.

TABLE 2

Liquid Medium (production media)

	Liter
Potato starch	8 g
Yeast extract	2 g
Defatted soybean flour or meal	2 g
Fe(III)EDTA	0.008g
$MgSO_4 \cdot 7H_2O$	1 g
$CaCl_2 \cdot 2H_2O$	1 g
HEPES	11.5 g
Glucose	2 g
pH medium with KOH to 7.4	

SF Medium

	Liter
Peptone	1 g
KNO_3	2 g
K_2HPO_4	0.125 g
Fe(III)EDTA	0.008g
$MgSO_4 \cdot 7H_2O$	1.5 g
$CaCl_2 \cdot 2H_2O$	1 g
HEPES	11 g
Fructose	5 g
pH 7.4	

III. Cloning and Characterization of the Disorazole PKS Genes

[0088] Of approximately 600 drug resistant colonies screened, one showed no production of disorazole A and was grown up in SF medium. Chromosomal DNA was extracted according to published procedures (Jaoua et al., 1992, "Transfer of mobilizable plasmids to Sorangium cellulosum and evidence for their integration into the chromosome" *Plasmid* 28:157-65). The purified chromosomal DNA was subjected to partial SauIIIA digestion, ligated into the pKOS cosmid vector, and packaged into lambda heads using the Gigapack III XL packaging extracts (Stratagene).

[0089] To isolate cosmids containing the transposon (and the flanking chromosomal DNA), three μl of the packaged DNA was infected into XL1BlueMR, allowed to grow for an hour and then plated on LB plates containing phleomycin. Seven drug resistant colonies were isolated and cosmid DNA was isolated. Cosmid DNA was sequenced using primers that hybridize to the T3 and T7 promoter sequences present in the seven cosmid vectors at the sites immediately flanking the insertion, to obtain sequence at the ends of the inserts. Two of the cosmids, cosmids pKOS254-190.5 and pKOS254-190.6, had identical inserts. Table 3 summarizes the sequences obtained with reference to SEQ ID NO:1.

TABLE 3

COSMID (and end sequenced)	Corresponding region of SEQ ID NO: 1	
pKOS254-190.1 *T7 end*	76928	77266
pKOS254-190.1 *T3 end* (KS domain)	34221	33420
pKOS254-190.2 *T7 end*	73132	73931
pKOS254-190.4 *T7 end* (KS domain)	51198	51460
pKOS254-190.4 *T3 end*	3007	3725
pKOS254-190.7 *T3 end* (KS domain/DH domain)	29496	30288
pKOS254-190.5/pKOS254-190.6 *T7 end* (KS domain)	43507	44330
pKOS254-190.2 *T3 end* (KS domain)	33426	33765

[0090] Cosmid pKOS254-190.2 contained an artifactual rearrangement at the T3 end. The "T3" ends of pKOS254-190.5/pKOS254-190.6 and pKOS254-190.3 and the "T7" end of pKOS254-190.7 T7 included sequence in the region flanking SEQ ID NO:1

[0091] The relationships of the clone inserts are shown in Figure 2. Sequences characteristic of KS domains were identified in each of the clones, as indicated. The "CSSSL" motif characteristic of KS domains was found in the partially sequenced KS domains of pKOS254-190.1 and pKOS254-190.2. Interestingly, sequence analysis of pKOS254-190.7 revealed a ketosynthase (KS) domain adjacent to a dehydrogenase (DH) domain, with no intervening actyl transferase (AT) domain. This suggested that the AT activity is supplied by an AT encoded as a separate protein, rather than existing as domains in each of several modules.

[0092] The gene sequence flanking the transposon insertion site was also determined using primers 66.2 (GGACGGGACGCTCCTGCGCC [SEQ ID NO:2]) and 66.1 (CTTTAGCAGCCCTTGCGCCC [SEQ ID NO:3]). The site of insertion at the TA dinucleotide at bases 50,232 and 50,233 of SEQ ID NO:1. Based on sequence analysis, the site of insertion is an NRPS oxidation domain, which is bracketed by a KS domain and a PCP domain, as shown in FIGURE 2.

Sequence of cosmid pKOS254-190.4

[0093] Cosmid pKOS254-190.4 was partially sequenced and the sequence was assembled into 21 contigs. Table 4 summarizes the sequences obtained with reference to SEQ ID NO:1. Table 5 shows differences between the initial sequences (e.g., due to sequencing errors or gaps) and SEQ ID NO:1.

TABLE 4

Contig	Corresponding region of SEQ ID NO: 1		Comment*
Fused M&T Contigs	32774	34331	192 . . . 1490: predicted ketosynthase domain
Contig L	38589	42122	2 . . . 532: predicted C-terminal region of a ketosynthase domain 1151 . . . 1624: predicted dehydratase domain" 2705 . . . 3481: predicted ketoreductase domain"
Contig I	29496	31763	701 . . . 1108: predicted dehydratase domain"
Contig G	22833	25082	106 . . . 288: ACP3; predicted acyl-carrier-protein domain 499 . . . 1794: KS4; predicted ketosynthase domain
Contig F	17740	22733	90 . . . 806 (predicted S-adenosyl-methionine-dependent C-methyltransferase)

			1029 . . . 1238 (predicted acyl-carrier-protein domain) 1752 . . . 3020 (KS3; predicted ketosynthase domain) 4290 . . . 4994 (KR3 (nter); predicted N-terminal region of a ketoreductase domain)
Contig E	12912	17613	1 . . . 582 (predicted C-terminal region of a ketoreductase domain) 709 . . . 913 (ACP1; predicted acyl-carrier-protein domain" 1156 . . . 2430 (KS2; predicted ketosynthase domain) 3761 . . . 4702 (DszB (nter)) 3803 . . . 4483 (KR2; predicted ketoreductase domain)
Contig D (Rev. Comp.)	11008	12229	105 . . . 548 (DH1; predicted dehydratase domain)
Contig C	8215	10980	98 . . . 1228 (KS(cter); predicted C-terminal region of a ketosynthase domain)
-"NRPS" Contig	47894	51480	
Contig A	34422	37725	
Contig B	6941	8030	
Contig J	34422	35623	
Contig OP	43797	46757	
Contig Q	27043	28235	
Contig R	28472	29490	
Contig 19 Ends	42774	43658	
Contig 20 Ends	42332	42764	
45-20	25808	26716	
46-48	4301	5161	
4T3	3009	3754	

* The base pairs indicated in the comments correspond to the numbering of the original sequence obtained. For example, base pair 2 of Contig L is basepair 38591 of SEQ ID NO:1.

TABLE 5

DNA fragment	Seq ID No.	Nucleotide of SEQ ID NO:1	Nucleotide of DNA fragment	Change**
Contig B	40	6941	1	G->C
		6945	5	insert C
		6946	6	G->C
		6949	9	A->T
		6953-6954	14	Remove G
		6956	17	C->T
		6957	18	G->C
		6958	19	A->G
		6961	22	A->G
		6962	23	C->A
		7914	975	A->G

		7962-7963	1024	Remove A
Contig C		4242-8243	28	Remove A
		8296-8297	83	Remove N
		9925	1713	C->G
Contig D	33	11086	79	T->C
Contig E	30	16148	3237	G->C
		16150-16151	3240	Remove C
		16157	3247	A->G
		16227	3317	T->C
Contig G		25057-25058	2226	Remove G
45-20	48	25808	1	A->C
		26688	881	Insert A
Contig Q	43	28221	1179	T->C
contigNOP	42	44792	995-996	Insert G
		44797	1000	A->G
		44808	1011	C->G
		44811	1014	A->G
		44816	1018-1019	Insert G
		44826	1027-1028	Insert G
		44831	1033	A->G
		44855	1056-1057	insert C
NRPS	37	47898	5	T->C
		48780	887	S->C
		49515	1622	C->G
OX/KS	18	50202-50231	1-30	Remove bases Part of transposon
		51035	840	N->G
PCP/OX	17	50234-50273	707-752	Remove bases Part of transposon
190.2T7	14	73207	76	N->C
190.4T3	10	3007	1	G->C
46-48	49	5130	821	N->G
		5139-5140	831	Remove N
		5148	840	A->G
		5161	853	A->C

** The base pairs indicated correspond to the numbering of the original sequence obtained. For example, base pair 1 of Contig B is basepair 6941 of SEQ ID NO:1. The sequence resulting from the "change" corresponds to SEQ ID NO:1 (e.g., nucleotide 6941 of SEQ ID NO:1 is C).

[0094] The order of the contigs in the disorazole PKS is (in 5'->3' orientation) C-D-E-F-G-I-NRPS.

EXAMPLE 2

[0095] Additional sequence analysis was carried out using the pKOS254-190.1 and pKOS254-190.4 resulting in the complete sequence of the the disorazole synthase gene cluster

and flanking regions as provided as SEQ ID NO:1 (Table 6). This 77,294 bp sequence includes the *dsz*A, *dsz*B, *dsz* C, *dsz*D coding sequences and several other open reading frames. Figure 3 shows the three proteins encoding modules 1-8 of the disorazole PKS gene cluster. *dsz*A encodes modules 1, 2, 3 and part of module 4. *dsz*B encodes the remainder of module 4 and modules 5, 6 and 7. *dsz*C encodes module 8.

[0096] As is discussed above, the acyltransferase (AT) activity used in disorazole biosynthesis is not encoded by *dsz*A, *dsz*B and *dsz*C, but instead is expressed as a distinct polypeptide, designated *dsz*D. Figure 4 shows the organization of the AT/oxidoreductase bidomain protein. The coding sequence for the AT/oxidoreductase bidomain is located downstream from *dsz*C in pKOS254-190.1.

TABLE 6
Disorazole PKS

77294 BP SS-DNA

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       1 TGGGTATCCC GAGCCGCTGG CGCCGTTCCC ACAAGGCCTT GCGGCTGATG CCGAGCCGAC
      61 GGGCAATCTC GGTCTCCGTC AGCTCGTCCT GGTGCTCCAG CACGAAGCGG CGGAAATAGC
     121 CCTCGAGCGA GTCCGAAGGC GGCGCCCCGT CGCGCAGCGA TGCGGAGGAG ACGGGCGGAG
     181 GCGGCCGCGG CGGGTCGTCG AGCCCGAGGT GGGCCCTCTC GATCGCGCTG CCCCCGGCGA
     241 GCACCACGGC GCGGTGAACG GCGTTCTCCA GCTCCCGGAC GTTGCCCGGC CACGGCGCCG
     301 CCGCGATGGC CGCGCGCGCC TCCGCCGACA GCGCGAGCGG CGCCTGCCCC ATCACCCGCG
     361 TCCGTCGCTT CAGCAGCGAC TCGGCGATGC GCACCGCGTC CCCGGGCCGC TCCCGCAGCG
     421 GCGGCAGCCG GATCTCCAGC ACCCGCAGCC GGAAATACAG GTCGCTCCGG AAGCTCCCCT
     481 CGCGCACCAT CGCCCCGAGA TCCCGGTGCG TCGCCGCGAT CAGCCGCACG TCCGCCCGCC
     541 GGGCGCGCGT CGACCCCACC CGCCGCACTT CGCCCGTCTG CAAAAAACGC AGCAGGCGCC
     601 CCTGCACCTT CATCGGCAGC TCGCCGACCT CGTCGAGCAG CAGCGTCCCG CCCTCCGCCG
     661 CCTCGCACAG CCCCGCCCGC GCCGCGAGCG CGCCCGCGGC CGCGCCGGCC TCGTACCCGA
     721 ACAGCTCGCC CTCGATCTGC GCATCGGGGA TCGCCGCGCA CTGCACGAGC ACGAACGGCT
     781 GCTGCCGCCG CGGGCTCAGC CGGTGCACCG CGCGCGCCAG CGTCTCCTTG CCCGTGCCCC
     841 CCTCGCCCAC CACCAGCAGC GTCGCCTCGC TCGGCGCCAC CTTGCGCACC TGCGCGAACA
     901 CCTCTCGCAT CGCCGCAGAG CCGCCCACCA TCCCCTCGAG CTCGTCGCCG TCCGGCGCCG
     961 GCGGCGCGGG CGGCGCGGCC AGAGGCGCGG GCGGCGCGGC CTCGGGGCGC ACGCTGGCGA
    1021 GGTGGCGCTC GACAAGCGCG ACGAGCTCGT CGTGATCGAA CGGCTTCGAG AGGTAATCCG
    1081 CCGCGCCCCG CTTCACGGCC TCCACCGCCG CCTTCACGGT CGCATAGCTC GTCATCAGCA
    1141 CCACCGGCGC GCTCCCGCAC CGCCCCACGA GCTCCGTCCC CGGCGCGCCG GGCAAGCGCA
    1201 CGTCCGCCAG CACCAGATCG AACGCGCAGA GCTCGTGCTC CGCCTCCGCC TCGGCGATCG
    1261 ACCCCGCCTC GACGACGGCG TGCCCGTGGC GCGCCAAGAG CCGCCGCAGC TCCGCACGGA
    1321 TGACGATCTC GTCCTCGATC AGCAGGATCC GGCTCATGCT TCCACCTCGC GCCCGCGCCG
    1381 CGCCCCGGCC TCGCCCGCCA GCGGGAGCCG CACGATCACC GTCGTCCCCT GCCCCACCGC
    1441 GCTCCGCAGC GCCAGCGCGC CGCCGTGATC CTCGATGATC GAGCGCGAGA GCGGCAGGCC
    1501 GAGCCCGGTG CCGCTCGGGT CGCGCTTCGT GGTCACGAAC GGCTCCAGCA CCGCGGAGAG
    1561 GAGCTCCTCG GGGATGCCGC TGCCGTGGTC CTCGACCTCG ACGACGATCT GGCCCGCCTC
    1621 GATCCACCCG CGGACGGCGA CGGTCGCGCC GGGCTCGGAC GCGTCGCGGG CGTTCGCGAG
    1681 CAGGTTCACG AAGACCTGCA CGAGCTCGCG CCGGTCGCCG ATGACAACGA GCGACTCCGG
    1741 GCAGTGCTGC TCCACCCGCA CGTGCGGGGC CGTGCGGTCG AGCCGGATCA GCCGATCCGC
    1801 CTCGGCCACC ACCTCGGCGA GCGACACGCG ACCGACCCGC GCGCGCGGGA TCTCGCCGGG
    1861 CGACGGCACG GCGCCGGTGC GGCTGTGATC GAGCAGCGAC CGGAGGATCG CCTCGATGCG
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1921 CGCCGTCTCG CCGAGGATGA GGCCCGCCCG CGCGCGGATC TCGTCGCTGT CGGCCTCGGC
1981 CCGGAGGTTC TGCGCGAGGC AGGCGATGCC GGTGAGCGGG TTGCCGACCT CGTGGGCCAC
2041 GCCCGCGGCG AGCCGCCCGA TCTGGGCCAG GCGGTCGCGG TGGGCGAGCT GCGCCTCGAG
2101 CGCGCGCTGC TCGGTGCGAT CCTCCACGAG CAGGACCACG CCGCCCGAGG CGGCCCGCGC
2161 GTCGAGCGGA TCGAGCGCGG CCCGGTGCAC GCGCAGGAGG CGCGCCCGCC CGGCCACGAG
2221 CACCTCGATC TCCTCGGCGC CCGCGCCGGC CTCGCCCGCG GAGGCCGCGC GGGCCGCGCG
2281 GGCGAACAGC TCCGCGAACG GGGCCGGCAG CCGGTCGAGC GGCGCCCCGA CGAGGTCGCG
2341 CTCCTCGGCG CCGACGAGCG CCTCGAGGCG CCGGTTGACG AGGCTGATCG CGCCGTCGGA
2401 GCCCACGGCG CAGACCCCGA GAGGGAGCTG CGCGAGCACC GAGCGCAGCC ACCGCCGCAG
2461 GAGATCGAGC TCCCTCGCCG CGCCGACGAG CCGCGTCTCG CCGCGCGCGA GGCGCCGCTC
2521 CAGCCACCGG AGCTCCTCGG TGAGCGCGCC GGACGCGCCG CCGGACGCGA CCGGCGCGCT
2581 CGCCTCCGCC TCCGCCGCCG TCCTCGCGAG CACCGGGCCG ACCAGCGGCG ACAGGTTGCG
2641 GTGCAGCCGC TCCTGCAGCG CGTGGAGCTC GGTGGGCCGC GTCTCGTCGC GCGAGATGTC
2701 GAGCTCGATC CGGGCGCGCG TGACCTCGAT CGCGGCCGCC TCGCGGCCGA GCAGCCGCGC
2761 GAGCCTGTCC TCCAGCGCGG CCACGCTCGA CGCCACGGTC GCGCGCTCCA CCGAGGGGCC
2821 GATCTCGCGG CGCGTGCACA GGCGGGCCGC CTCGCGCTCC TCCCTGGCCG GCGGGCGCAG
2881 CAGCGAGACG ATCCCGAGCG TCGCGCCGTT GACGGCGAGC GACACGAACG TCGGGAGCGA
2941 CCACGGGTCG ATGGGCGCCG CGCCCGCCGG CGCGCCCGCG CCCCCGCGCA GGAGCGCGAG
3001 CCACGCCGGA TCGATCCCGG GCACGCCGGG CAGGAGCGGC GCGAGGCAGG TGGCCGTCCA
3061 GGTCGCGATG CCGGCGAGGA GCCCGGCCAT GAACCCCGCG CGCGTGGCGC GCTCCCAGAA
3121 GAGCGCGGCG AGCAGGCCCG GGAGGAACTG CGCGAAGGCG ACGAACGACA CGATGCCGCT
3181 CTCGACGAGC AGCCCGTGGT GCGGCTGCGC GCGGTGGAAG AGCCACCCGC CGACGAGGAT
3241 GGCCGCGAGG AGCACGCGCC GGAGCCACAG CACGCGCGCG TACACGTTGC GGCGCAGCGT
3301 CCGCCGCGCG AGCGGCAGGA GCAGGTGCGT CGCGCTGTCG TTCGCGAGGG CGACGGCCGT
3361 GACCATGGCC ATGGCGCTCG CCGCGGAGAT GCCGCCGATG AACGCGGCGA GCGCGAGCCA
3421 GCGCTGGCCG AGCAGCTGCG GCACGAGCAG CACGTAGCTG TCGGCGGGCT CGGCCGGGGC
3481 GAGGCGCGTC CCGGCCCAGA GGACGGGCAG GACGGGCAGG TTGAGCGCGA GCAGGAACAG
3541 GGGGAACGCC CACGCCGCCG TGGCGAGCGC GCGGTCCCCG GCGCCGCTGG CGAACGCCAT
3601 GTGCCACTGC CGCGGCAGCA GGAAGGCCGC GGCGAAGCTG ATGACGAGCA TCGAGGTCCA
3661 GCCGCTGTCC TCCCGCACGT GGCGGCCGAG CGCCTCGACC TCGGCGGCGT GCTCGCCGAG
3721 CCAGCCCGCG AGCCCGCCGA GCCCGCCGAA CGCCCCGAGC ACGGCGGCGA GGCCCACGGC
3781 CGCGAGCACG GCGAGCTTCG CCGCCGACTC GAACGCGACG GCCGCCGCGA GGCCGTCCTC
3841 GCGCCCCTGC TCGGCCGACG GGCGGGCGCC GAAGAAGGCC GTGAAGAGCG CGAGCAGCGC
3901 GCAGAAGACG GCGCCCACGG CCTCCTCGTG CCCCGGCCCC GAGAGCACGC GCACCGACTG
3961 CACGGTCGCG CGGAACTGCT GCGCGACGTA GGGCAGGCTC GCCACGAGCG CGAAGGCGGC
4021 GACGAGCGCC CCGGCGGCGG GGCTCTGGAA GCGGAACGCG AGCAGGTCGG TGAGCGACGA
4081 GAGGCGCTGC TCGCGCGTGA TGCGCAGCAC GCGCGCCCAG AGGAGCGGCG TGGCCATGCA
4141 CGCGAGCGTC GGGCCGAGGT ACACAGCGAG GAAGACGAGC CCGTGGCGCT GCGCGAAGCC
4201 GACGCCGCCG TAGTACGTCC ACGACGAGGC GTAGACGCCG AGCGAGAGGG CGAGCACGAG
4261 CGGGCTCCGC GCGAGCGCGC GCGGGCGCCG GGCGCGCTGC GCGGCGAGCG CGATCGCGGC
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75661 CGGGTCGACG AACCCCCGCC TCTTGAAGGG GATCGGCGAC GGATACCTCG CGGTCTATCC
75721 CACCATGACG CGCGCGCTCG ACGCGGCCCG CGTGCTCCGC GACGCGGTCG ACGACCCCGC
75781 CGAGCTCCGC CTCGTCCTGC ACTGGGGCGC GGTGCGGATG AGCGATCACG ACGTGATCGG
75841 CAGGGAGGTC CACCGGCTCT TCCGGATCGA GGCGGTCACC GAGGAGGATC GCGCCGCGGA
75901 GTCGAGCGCC GGGATCACCC TCGCGCAGCC CGGCCGGGTG AGGCTCTCGC GGCCCGCGCT
75961 CGCCGCGCTG CCCGACGCCG AGCGCGCGGG CTTCCGCCGG GCGGGGGCCT TCCGGCTGGA
76021 GGGGTTCGAC GAGCCCGAGC CGATCTGGGT GGAGATCGGC GCGGGCCGCT GAGGTCGCGC
76081 GGGCTACGGG GCGACGCGGA GCGTCCGCGA GGCGACGAGC GCCCGGCAGA GGGCGATCCG
76141 GTCGTCGAGG TCGAGGCCGG GGAGCTCGCG CACGTAGAAG ATGCCGTGCC GCGCGATGAA
76201 GCGGAGCGCG GCCTCCCCCC GCAGATCGAC GCGGACGAGC ACGGCCTCGC CGTCGACGAG
76261 CTCCGCCTTG CCGTCCCTCA GCCGGACCGA CGCCTCGCGA TCGCGGATCA CGCGCCGCGG
76321 GCCGCACACG GACGCCGCGT CGCTCCACAC CGCGGGCGGC GGCTCGCCGT AGAGGGCGCT
76381 GTACGCGGCC ACGAGCTCGT CCCATGTCGC CTCGCGGCGC GCGCCCGCGG CCGGCGCGTT
76441 GCTCGGCGCG TGGTGCAGGA AGCGCCCGAA GAAGCGCCGG CAGAACTCGG CGTATTCGAG
76501 CGTGAAGAGG GCGAACTGGT GCCAGGCCTC GTCGACGCGC AGCGAGAACA TCGGATAGGC
76561 GCGGGAGCGG TCGATCTCGA CGAGCCAGAG ATAGCGCACG AGCTCCCGGA ACAGCGCCTC
76621 TGCCTCCTCC CGGGTGGCCA CGGTCTTGTT CATGAGCAGC TTGTCGATCA CGAAGGGCGC
76681 CCGGTAAGCG AAGAGATCAG GCGTCCTGCG CTGGGTCGCG GTCACGATGT CCGTTTGCAT
76741 GGGTCAGTTC TCCTGGGCTT CGAGCGGCTG AAAGGTGCCG TGATCGACGA GCGCGCGGGC
76801 GAGCGCGAGC TGCTCGGCCT CGGCGAGGCC GGGGATGTCG CGGGGGCGGA GCTCGCGGGC
76861 GGCGGCGAGC GCGCGGAGCG CGGGCGCGGC CCACGCGTCG ACGCGGAGCA GGACCTGGGC
76921 GCGCTCGCCC GCGCGCGCGA GCAGCTCGGC GCGGCCGGCG CTCGACGCCA CGTCGAGGTC
76981 CACGCCCGGC CAGCGGCGCG CGAGGGCGGT CTGCGCGTCG AGGTCCTCCG TCCGGCCGAG
77041 CGCGCGGGCG GCGCGCCGCT TCGTCCCGGC GTCGCCGCGG GCGTGCAGGC GCGCGAGGAG
77101 CGCGGCGGCC CGCGGCCCCC TCCGCTCGAG GGCGTCGATC TGCGCCCGGC GCACGCGCTC

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77161 GCGGGCGTGC GCGTGGAGCG CCTCGGACAG CGCGTCCTCG GGGGCGGGCG GCGGCGCGGC
77221 GCCGGTCAGG CCGTCGATGG GGCCCACCTG CGCTTCCAGG ACCGGACCGT CGTGGGGGCC
77281 GAGCAGGTGC AGCG
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[0097] Earlier versions of the sequence of *dsz*A, B, C and D differed from SEQ ID NO:1 due to minor sequencing errors and/or small gaps in sequence. SEQ ID NO:1 ("version 1") is 77,294 bp in length. "Version 2" was 53,366 bp in length and corresponded to basepairs 3009 to 56,374 of SEQ ID NO:1. (The version 2 sequence differed from SEQ ID NO:1 at position 9925/6920 which was C.) "Version 3" was 53,784 bp in length and corresponded to basepairs 3009 to 56374 of SEQ ID NO:1. Version 2 differed from version 3 as shown in Table 7.

[0098] The invention provides polynucleotides having the sequence each of the DNA sequences disclosed herein, including the version 1, 2, and 3 sequences, fragments (such as described in Table 4).

TABLE 7

Seq ID NO:1 nucleotide no.	Change
28756..29032	"gap #1 in ver. 3 (ver. 3 estimate: approx. 300 bp; length found: 277 bp)"
42790..42790	"G->C; (ver. 3 G->ver. 2 C)"
43750..44079	"gap #2 in ver. 3 (ver. 3 estimate: approx. 300 bp), together with ver. 3 adjacent 37 bp: [GGCCCGACGGGCCGTGCGCCGCGCCGCGGTTCTCTTT], replaced here by a total of 330 bp"
44092..44092	"T->C; (ver. 3 T->ver. 2 C)"
44166..44167	"C->CC; (ver. 3 C->ver. 2 CC)"
44169..44169	"T->C; (ver. 3 T->ver. 2 C)"
49623..49623	"T->C; (ver. 3 T->ver. 2 C)"
49690..49691	"GG->CT; (ver. 3 GG->ver. 2 CT)"
49702..49702	"A->C; (ver. 3 A->ver. 2 C)"
50603..50603	"TT->T; (ver. 3 TT->ver. 2 T)"
50694..50694	"G->C; (ver. 3 G->ver. 2 C)"
50719..50719	"GG->G; (ver. 3 GG->ver. 2 G)"
50739..50739	"T->C; (ver. 3 T->ver. 2 C)"
50760..50760	"N->C; (ver. 3 N->ver. 2 C)"
50773..50773	"GG->G; (ver. 3 GG->ver. 2 G)"
50829..50829	"N->C; (ver. 3 N->ver. 2 C)"
50956..50956	"N->A; (ver. 3 N->ver. 2 A)"
50973..50974	"TC->CT; (ver. 3 TC->ver. 2 CT)"
51005..51005	"N->G; (ver. 3 N->ver. 2 G)"
51043..51043	"C->A; (ver. 3 C->ver. 2 A)"
51050..51050	"C->T; (ver. 3 C->ver. 2 T)"
51066..51066	"GC->C; (ver. 3 GC->ver. 2 C)"
51070..51070	"C->A; (ver. 3 C->ver. 2 A)"
51119..51137	"24 bp->19 bp; (ver. 3 24 bp: ATGAGGCGACAGCGCCGTTCTACC, replaced by 19 bp: TGAGGGACAGCCCGTTCTA)"

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51160..51160     "C->T; (ver. 3 C->ver. 2 T)"
51208..51208     "CC->C; (ver. 3 CC->ver. 2 C)"
52170..52170     "T->G; (ver. 3 T->ver. 2 G)"
53366..53366     "truncation; in the ver. 3 sequence,
                 this base was followed by an additional 379
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EXAMPLE 3

MYXOCOCCUS XANTHUS HOST CELL EXPRESSING THE DISORAZOLE PKS AND CAPABLE OF PRODUCING DISORAZOLE

[0099] This example describes creation of a *Myxococcus xanthus* host cell expressing the disorazole PKS and capable of producing disorazole. Briefly, a *Sorangium cellulosum* genomic library is screened using probes from the *S. cellulosum* disorazole NRPS oxidation domain coding sequence of pKOS254-190.4. A genomic clone encoding the complete NRPS oxidation domain plus those disorazole PKS modules and accessory proteins not encoded by pKOS254-190.1, is selected and referred to as pKOS254-190.8. pKOS254-190.4 and pKOS254-190.8 are introduced into *M. xanthus* by homologous recombination using established methods, resulting in a complete PKS gene cluster. The host cells are fermented and produce disorazole.

[0100] To obtain pKOS254-190.8, a cosmid library is screened using a ^{32}P-labeled probe generated by PCR amplification of pKOS254-190.4 using primers 249-179.1 [5'-AGGAAGAGCTCCAGCGCA-3'; SEQ ID NO:4] and 249-179.3 [5'-ATGAAGCTGATCCAGACC-3'; SEQ ID NO:5]. The probe has the sequence 5'-

AGGAAGAGCTCCAGCGCATCCTCGGCAAGGCGCTGCACCTCACCCGCCTCGATCCCGGCGCTGACCTCTTCGAGCTG
GGCGCCACCTCGCTCACCATCGTGCAGGCGTCACAGCACATCGAGGAGCGCTTCGGCGTCGGGCTGCCGGTCGAGGT
CGTCCTGGCCGAGCCGACCCTCGACGCCATCGCGCGGCACGTCGCCGAGCGGACGGCGGCTGGCGCGCCCGAGCCCC
CGGCCCCCGGGCCCGCGCTGGACGCGCCTCCCGCGGCGCCCGAGCCCCCGGCCGCCGCCGCCCCCGGCCCGATCGAT
TTCTTCTCCAGGGAAGATCGGGAGCGCTTCAAGCAGCAGCAGCTCCACCTGCGGCACGGCGTCGAGGGCCTCCCGAC
CGTGGATCTGGCCGACGCTCCCGCGGCCCCGCGCCTCTACCGCGACCGCGGGAGCCGCCGCGACTACCGGCCCGAGC
CCGTCTCGTTCGACGACCTCTCGCGCCTCCTCGCCGTCCTCCGGCGGTACCCGAGCGGCCAGCAGACCCAGCTCTGC
TATCCCTCGGCCGGCGGCACCTACGCCGTGCAGACCTATCTTCACGTGAAGGAGGGCGCGGTCGAGCGCCTCCCGGC
CGGGATCTACTACTACCACCCGGATCGCAACCAGCTGGTGCTCATCAACGATCGGCCCGCCATCCGCCGGGTGCACC
ACTTCTAACAGGTTGGCTGATAAGTCCCCGGTCTGGATCAGCTTCAT [SEQ ID NO:6]. A cosmid library was made from So ce12 chromosomal DNA following the manufacturer's protocol (Stratagene, Inc., La Jolla, CA). To obtain *Sorangium cellulosum* genomic DNA, *S. cellulosum* So ce12 cells

were grown in a fructose based medium to obtain dispersed growth of the strain. The dispersed-growth medium composition used is: $MgSO_4 \cdot 7H_2O$, 015%; $CaCl_2 \cdot 2H_2O$, 0.1%, KNO_3, 0.2%; K_2HPO_4, 0.0125%, fructose, 0.5%, Na-Fe-III-EDTA, 8 mg/L, peptone from casein, tryptically digested, 0.1%, HEPES, 1.1%. The medium was adjusted to pH 7.4 with KOH. Chromosomal DNA was isolated from 5 ml of So ce12 culture in stationary phase. The cells were pelleted and resuspended in 1 ml of STE buffer (25% sucrose, 10mM Tris pH8.0, 1 mM EDTA) and lysed with 200 µl of rapid lysis mix RLM (5% SDS, 0.5 M Tris pH7.6, 125 mM EDTA), mixed by inverting the tube several times, and then incubated at 65-70°C for 30 minutes or until the mixture cleared. The mixture was then neutralized with 200 µl of 5 M potassium acetate and vortexed until thoroughly mixed. The tube was centrifuged for 10 minutes and the supernatant was removed. The mixture was then extracted with 500 µl of TE-saturated phenol, and the solution vortexed several seconds. The tube was centrifuged and the bottom DNA-containing layer was removed. Two volumes of 100% ethanol were added and the tube was inverted several times until the DNA precipitate was visible. The DNA was pelleted and then washed with 70% ethanol. The DNA was resuspended in TE.

[0101] A cosmid containing the complete oxidation domain and those disorazole genes absent from pKOS254-190.4 is isolated and called pKOS254-190.8. pKOS254-190.8 and pKOS254-190.4 are recombined into the *M. xanthus* chromosome using regions of homology from these cosmids to reconstruct the disorazole gene cluster, analogous to the method described (for the epothilone PKS gene cluster) by Julien and Shah, 2002, "Heterologous expression of epothilone biosynthetic genes in *Myxococcus xanthus*" *Antimicrob Agents Chemother.* 46:2772-8, incorporated herein by reference. Also see U.S. Patent 6,410,301, incorporated herein by reference.

EXAMPLE 4

MYXOCOCCUS XANTHUS HOST CELL EXPRESSING A DISORAZOLE PKS OBTAINED BY BAC CLONING

[0102] This example describes cloning of a bacterial artificial chromosome (BAC) encoding the complete disorazole gene cluster. The BAC is introduced into *M. xanthus* by conjugation, for integration into the *M. xanthus* chromosome.

[0103] A *S. cellulosum* bacterial artificial chromosome (BAC) library containing an average insert size of 100 kb was prepared by standard methods (Amplicon) and Probe 249-179 (Example 2) is used to screen for a BAC containing the complete disorazole gene cluster. The BAC, referred to as pKOS254-190.9 is integrated into a phage attachment site using integration functions from myxophage Mx9. A transposon is constructed that contains the attP site from Mx9 along with the tetracycline gene from pACYC184. The necessary integration genes are supplied by a *M. xanthus* strain that expresses the integrase gene from the *mgl* (constitutive) promoter (see Magrini et al., 1999, *J. Bact.* 181: 4062-70). Once the transposon is constructed, it is transposed onto pKOS254-190.9 to create pKOS254-190.10. This BAC is conjugated into *M. xanthus*. This resulting host contains all the disorazole genes as and corresponding *Sorangium cellulosum* PKS gene promoters (which have been discovered to be active in *Myxococcus*). This strain is fermented and tested for the production of disorazole A.

[0104] Although the present invention has been described in detail with reference to specific embodiments, those of skill in the art will recognize that modifications and improvements are within the scope and spirit of the invention, as set forth in the claims, which follow. All publications and patent documents cited are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any such document is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description and example, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples are for purposes of illustration and not limitation of the following claims.